REMARKS

At the outset, Applicants thank the Examiner for her thoughtful comments during the March 31, 2008 telephonic interview with Applicants' representatives, Dr. Lindeman and Ms. Webster. SUBSTANCE OF THE INTERVIEW: During that interview, the parties discussed amending the pending claims (58, 71, and 73-76) to clarify that the pattern of binding on an array arises not from dilutions of markers, but from each region being specific for a single cell surface marker presented only once in the array. The parties also discussed amending the claims to reflect that the solid support is not the glass cover slip of the prior art (Chang, Brandt, and Ceriani), but a derivatised solid support, for example a glass slide coated with nitrocellulose. Applicants also acknowledge with appreciation the Interview Summary mailed April 4, 2008.

Claims 1-57, 59-70 and 72, were canceled previously, without prejudice to the subject matter contained therein. Claims 58, 71, and 73-76 are pending. Claims 58 and 71 have been amended, new claim 77 has been introduced herein. Support for the amendments and new claim may be found throughout the specification, for example at Example 1, Example 9, and Figure 5.

In particular, claim 58 has been amended to read:

58. (Presently Amended) An assay device for distinguishing a leukemia of T-cell, B-cell, or myeloid lineage in a subject, said device comprising

(a) a derivatised solid support; and

(b) an array of immunoglobulin molecules, or antigen-binding fragments thereof, immobilized in discrete regions on the derivatised solid support, wherein the immunoglobulin molecules, or antigen-binding fragments thereof, are specific for single distinct cell surface marker antigens comprising CD3, CD4, CD8, CD14, CD19, and CD56 on a leukocyte, such that specific binding of the immunoglobulin molecule, or antigen-binding fragment thereof, of each discrete region to its respective distinct leukocyte cell surface marker antigen provides a pattern of binding on an array of discrete regions, each being specific for a single cell surface marker presented only once in the array, of the different leukocyte cell surface marker antigens comprising CD3, CD4,

CD8, CD14, CD19 and CD56, that distinguishes leukemias of T-cell, B-cell, or myeloid lineage.

Rejections under 35 U.S.C. § 112

On page 2 of the Office Action, the Examiner rejects claims 58, 71, and 73-76 under 35 U.S.C. § 112, second paragraph "as being indefinite." More specifically, claim 58 recited "immunoglobulin" rather than "immunoglobulin molecule," the former lacking proper antecedent basis. Claim 58 has been amended to the proper recitation, hence the rejection which may now be withdrawn.

Rejections under 35 U.S.C. § 102

On page 3 of the Office Action, the Examiner rejects claims 58, 73, and 75 under 35 U.S.C. § 102(b) "as being anticipated by Chang (Journal of Immunological Methods, Volume 65, 1983, pages 217-223)." Applicants respectfully traverse the rejection.

Anticipation under 35 U.S.C. §102 requires every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim, and such reference must be enabling and describe the claimed invention sufficiently to place it in possession of a person of ordinary skill. *See, In re Paulsen*, 30 F.3d 1475, 1478 (Fed. Cir. 1994). Chang does not teach each and every limitation of the pending claims. For example, Chang does not refer to a device that provides a pattern of expression that distinguishes the lineage of leukemias. Indeed, Chang never mentions leukemia at all.

The Examiner, on page 4 of the Office Action, asserts that Chang refers to

"array comprises 7 to about 1000 discrete regions on the solid support, wherein each discrete region comprises an immunoglobulin molecule, or antigen-binding fragment thereof, that is specific for a single distinct cell surface marker antigen on a leukocyte such that the array comprises different immunoglobulin molecules, or antigen-binding fragments thereof, specific for different cell surface marker antigens, wherein the cell surface marker antigens are selected from the list in Table 4."

In contrast, Chang notes that "**if** antibodies of relevant but distinct specificities can be prepared and purified, they can be coated on a small area of a surface and be used to analyze antigens." Yet Chang used only one or two antibodies and two types of cells. In each instance,

the antibody and cell were known to interact before the experiment, thus Chang did not provide any test of wherein a cell sample of unknown character was identified by an antibody. More specifically, Chang does not disclose the claimed markers CD3, CD4, CD8, CD14, CD19 and CD56, or a ***pattern of binding*** on an array of discrete regions, each being specific for a single cell surface marker presented only once in the array, of the different leukocyte cell surface marker antigens comprising CD3, CD4, CD8, CD14, CD19 and CD56, that ***distinguishes*** leukemias of T-cell, B-cell, or myeloid lineage. Moreover, Chang used only glass cover slips, and never refers to the use derivatised solid surfaces. Hence, because Chang does not teach each and every limitation in the pending claims, it does not support a § 102 rejection. Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

On page 5 of the Office Action, the Examiner rejects claims 58, 73, and 75-76 under 35 U.S.C. § 103 "as being anticipated by Chang ... in view of Brandt et al. (U.S. 4,797,356)." Applicants respectfully traverse the rejection.

The present invention provides for an assay device for distinguishing a leukemia of T-cell, B-cell, or myeloid lineage in a subject, said device comprising (a) a derivatised solid support; and (b) an array of immunoglobulin molecules, or antigen-binding fragments thereof, immobilized in discrete regions on the derivatised solid support, wherein the immunoglobulin molecules, or antigen-binding fragments thereof, are specific for single distinct cell surface marker antigens comprising CD3, CD4, CD8, CD14, CD19, and CD56 on a leukocyte, such that specific binding of the immunoglobulin molecule, or antigen-binding fragment thereof, of each discrete region to its respective distinct leukocyte cell surface marker antigen provides a pattern of binding on an array of discrete regions, each being specific for a single cell surface marker presented only once in the array, of the different leukocyte cell surface marker antigens comprising CD3, CD4, CD8, CD14, CD19 and CD56, that distinguishes leukemias of T-cell, B-cell, or myeloid lineage.

The claimed device thus provides a pattern that provides a diagnosis in a single, rapid test, assisting clinicians to achieve a better understanding of their patient's condition and thus provide better treatment. Since the filing of the present patent application, this assay device has

been applied to the analysis of over 700 patients and has proved over 90% accurate when compared to traditional techniques. Applicant's award-winning technology has been also been commercialized in Australia.

The Examiner asserts, on pages 3-4 of the Office Action, that "Chang discloses an antibody matrix method using a solid matrix surface of an array of antibodies to determine the proportion of specific T-cell, B-cell, or monocytes in a mononuclear cell fraction ... and determining a specific allotype of a surface antigen on the cells of an individual and analyzing functionally different cell subpopulations that express distinct differentiation antigens ... and using human peripheral blood mononuclear cells ... which represents an assay device for identifying a leukemia of T-cell, B-cell, or myeloid lineage in a subject..."

This is not correct, however, Chang never mentions the application of the technique to any diagnostic screening or in particular to diagnosing between leukemias. As noted above, Chang posits that "**if** antibodies of relevant but distinct specificities can be prepared and purified, they can be coated on a small area of a surface and be used to analyze antigens." Yet Chang used only two antibodies and three types of cells. In each instance, the antibody and cell were known to interact before the experiment, thus Chang did not provide any test of wherein a cell sample of unknown character was identified by an antibody. Chang certainly does not provide for the immunoglobulin molecules for CD3, CD4, CD8, CD14, CD19, and CD56, of claim 58, to ***distinguish*** between T cell, B cell, or myeloid lineage leukemias. Indeed, Chang is completely silent regarding leukemia, and never mentions the application of the technique to any diagnostic screening or in particular to characterizing leukemias.

Moreover, the Declaration of Richard Ian Christopherson dated 28 September 2004, of record in the present application's sister case, Ser. No. 09/888,959 and provided herewith, states that the glass coverslips of Chang could not be used to effect the methods of the claimed invention because, *inter alia*, antibodies do not adhere reliably to plain glass slides, and because leukocytes bind to the glass itself causing high background. Christopherson Declaration at paragraphs 5 and 6. Indeed, the claimed method uses a derivatised solid support, thus avoiding these problems. Such derivatisation is explained in the specification at, for example, at the paragraph bridging pages 26 and 27 ([0122] of the published version), which states:

> The solid support is typically glass or a polymer, such as but not limited to cellulose, ceramic material, nitrocellulose, polyacrylamide, nylon, polystyrene and its derivatives, polyvinylidene difluoride (PVDF), methacrylate and its derivatives, polyvinyl chloride or polypropylene. ... A solid support may also be a hybrid such as a nitrocellulose film supported on a glass or polymer matrix. Reference to a "hybrid" includes reference to a layered arrangement of two or more glass or polymer surfaces listed above. The solid support may be in the form of a membrane or tubes, beads, discs or microplates, or any other surface suitable for conducting an assay. Binding processes to immobilize the molecules are well-known in the art and generally consist of covalently binding (e.g. cross linking) or physically adsorbing the molecules to the solid substrate.

Dr. Christopherson, at paragraph 5 of his Declaration, refers to such treated supports as derivatised rather than hybrid, but the meaning is clear to one of ordinary skill. Chang does not suggest derivatisation of the surface of the solid support, indeed because that technology was not available. *Id.*

Importantly, Chang states that, "it is possible that the matrix method can be used to determine the proportion of specific subsets in a mixed population, e.g., the proportions of B cells, T cells, and monocytes in the mononuclear cell fraction or the proportions of inducer and suppressor T cell in the T cell fraction." Chang, at page 223. Thus, Chang refers only to identification of ***cell types***, and not to the complex patterns of expression of markers that are associated with leukemia diseases. As Dr. Christopherson explained in paragraph 5 of the Declaration:

> The differential pattern of interaction indicates the relative density of interaction between each immunoglobulin and its cognate cell surface antigen, which may result, for example, from ***differential density*** of cells that bind to a discrete spot on the array, the ***differential expression*** of particular antigens, and/or the ***number of antigens*** per cell.

Moreover, Chang's statement that "It is apparent that the analysis of the cell binding results would be facilitated with proper instruments," hardly provides the suggestion of the claimed invention, given that such instruments were not in existence (Chang evaluated binding via "naked eye," see page 219, second full paragraph). In fact, the claimed assay device provides for a proper instrument. Indeed, the publication of Chang in 1983 supports the conclusion that

the claimed invention answered a long felt need to bring the claimed device to useful, commercial application for distinguishing between leukemias.

Regarding Brandt, this patent states "The antibody may be immobilized on appropriate solid supports or substrates such as microtiter plate wells or beads by adsorption or covalent bonding." But the only detailed discussion of such bonding is in "Protocol" which recites:

> A. Coupling of Antibody 3872 to Gel
>
> Carbodiimide-activated trisacryl gel GF-2000 (Pierce Chem. Co.) is washed twice with distilled H.sub.2 O and coupling buffer (0.1M borate, pH 8.5). Monoclonal antibody 3872 (2 mg) in 2 ml of coupling buffer and 2 ml of washed GF-2000 gel are incubated at 4°C overnight with shaking. Unreacted monoclonal antibody is recovered for reuse and unreacted active sites on the gel are blocked by incubation with 2 ml of 5% BSA in coupling buffer at 4°C overnight with shaking. The coupled gel is washed with 0.1M citrate, 1.4M NaCl (pH 4.0), 0.1M carbonate, 1.4M NaCl (pH 11.0) and finally CKT buffer (20 mM sodium cacodylate, 150 mM KCl 0.01% Triton X-100). Coupled gel is stored at 4°C in 5 volumes of 5% BSA, 0.05% sodium azide in CKT buffer. Estimate 1 mg McAb coupled per 1 ml gel based on recovered unbound protein.

Please note that Brandt does not suggest using a derivatised solid support.

The Examiner asserts that "it would have been obvious . . . to modify the assay device of Chang by immobilizing antibodies and antigen-binding fragments to a solid support by covalent binding as taught by Brandt et al. wherein the motivation would have been to perform a conventional immunoassay protocol to indicate the ***presence*** of cancer, including leukemia..." Office Action at page 6. The thrust of Brandt is that GT-II expression may be increased in a variety of diseases, including leukemia, but Brandt says nothing that suggests GT-II could be used to ***distinguish*** between types of leukemia. Indeed, there is no suggestion to combine Brandt with Chang. Moreover, as explained above, the performing a "conventional immunoassay" of the references does not suggest the claimed assay device.

The *In re O'Farrell* case is instructive on the present rejection:

> The admonition that "obvious to try" is not the standard has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many choices were likely to be successful. ... In others what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior

> art gave ***only general guidance*** as to the ***particular form*** of the claimed invention or how to achieve it. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988) (emphasis added).

Chang and Brandt, at best, provide only general guidance in a promising field of experimentation. The combination of these references simply does not suggest or provide for any expectation of an array of immunoglobulin molecules, or antigen-binding fragments thereof, immobilized in discrete regions on the derivatised solid support, wherein the immunoglobulin molecules, or antigen-binding fragments thereof, are specific for single distinct cell surface marker antigens comprising CD3, CD4, CD8, CD14, CD19, and CD56 on a leukocyte, such that specific binding of the immunoglobulin molecule, or antigen-binding fragment thereof, of each discrete region to its respective distinct leukocyte cell surface marker antigen provides a pattern of binding on an array of discrete regions, each being specific for a single cell surface marker presented only once in the array, of the different leukocyte cell surface marker antigens comprising CD3, CD4, CD8, CD14, CD19 and CD56, that distinguishes leukemias of T-cell, B-cell, or myeloid lineage. Applicants respectfully request that this § 103 rejection be withdrawn.

On page 6 of the Office Action, the Examiner rejects claims 58, 71, and 73-76 under 35 U.S.C. § 103 "as being unpatentable over Chang ... in view of Ceriani et al. (U.S. 5,514,558)." Applicants traverse the rejection.

The Examiner asserts that "it would have been obvious ... to modify the assay device of Chang by including covalent binding of polyclonal antibodies and fragments as taught by Ceriani et al. wherein the motivation would have been to provide a higher sensitivity and specificity that other assays, as taught by Ceriani et al. ..."

The assay of Ceriaini is a complex, competitive "sandwich" assay incomparable to the claimed device:

> In the present assay, an antibody raised against an antigenic peptide is attached to a solid support. Thereafter, a fusion protein of the antigenic polypeptide and an antigenic analyte whose presence is suspected in a sample, is incubated with the solid support-bound antibody and a sample to be tested. This permits for the fusion protein and the antigenic analyte present in the sample to compete for available binding sites on the

> antibody against the anti-antigenic peptide and bind to it. Thereafter, an antibody raised against the antigenic analyte is added and allowed to bind to the analyte and the analyte portion of the fusion protein, and the presence of a double antibody-fusion protein sandwich bound to a solid support is determined. The latter step can be implemented by adding a labeled antibody detecting molecule such as gamma-globulin or a fragment of the immunoglobulin labeled with an enzyme, a fluorescent tag and/or a radioactive atom. Other antibody binding or detecting molecules may also be utilized such as protein A or protein G, fragments and precursors thereof, or single antibody chains, such as heavy chains. Col. 9, lines 47-56.

The only context in which Ceriani discusses leukemia is in the Background of the Invention, and relates to polyclonal antisera reactive only against the non-penetrating glycoprotein (NPGP):

> Thus, although most of the above assays employing monoclonal antibodies detect the NPGP complex of the HMFG system, many of them may bind to different epitopes. A heterogeneity of epitopic expression may create the relatively small differences seen among different assays. The diffusely pan-epithelial nature of the NPGP complex as a marker was thus established as shown by its high circulating levels found in other carcinomas, melanomas and even in leukemia. The levels obtained varied depending on the units used in different immunoassays. The percent of positives found at different stages of breast cancer are similar to those originally reported with an assay using polyclonal antibodies to other components of the HMFG. An important drawback of the assays based on the detection of the NPGP complex using monoclonal antibodies is that they lack the specificity of polyclonal assays.
>
> A comparison of the specificities of the CEA assay, an assay detecting the NPGP complex using the Mc5 monoclonal antibody in an antigen displacement, and the original polyclonal antibody assay against HME antigens was made. The polyclonal antibody assay showed very high sensitivity and specificity. It yielded negative values for colon, ovarian, pancreatic, laryngeal and endometrial carcinomas, lymphomas, myelomas, melanomas, and leukemias. Only one case of lung carcinoma showed an elevated value. All normal serum controls were negative, thus showing this assay to have high specificity. Positive serum values for both the NPGP complex and CEA assays were not restricted to breast tumor patient's sera. Col. 6, lines 13-32.

Additionally, Ceriani does not discuss array devices of any kind, and refers instead to microtiter plastic wells (*see* Example 1, col. 19). Other than the mere presence of the words 'polyclonal' and 'leukemia' (in the Background section) there is nothing in Ceriani that suggests the claimed invention. As with Chang, there is nothing in Ceriani relating to an array that provides for a pattern of binding on an array of discrete regions, each being specific for a single cell surface marker presented only once in the array, of the different leukocyte cell surface

marker antigens comprising CD3, CD4, CD8, CD14, CD19 and CD56, that distinguishes between leukemias of T-cell, B-cell, or myeloid lineage. Indeed, the simplicity of the claimed array when compared to Ceriani's complex procedure points to the remarkable achievement of the claimed invention in the characterization of leukemias.

Hence, because this § 103 rejection is inadequately supported by the cited references, Applicants respectfully request that it be withdrawn.

Moreover, the Court has instructed that objective evidence relevant to the issue of obviousness, i.e., secondary factors, must be evaluated by Office personnel. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Such evidence may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. For example, that Chang published in 1983 supports a finding of long-felt need for the instant approach using an array on commercial scale.

Applicants invite the Examiner's attention to the MEDSAIC press release, which reports that Applicants' licensee received the 2005 "BioFirst Commercialisation Award" for outstanding achievement in technology for its leukemia and lymphoma diagnostic (submitted herewith). In addition to the recognition of commercial development and success in Australia, MEDSAIC was deemed most likely to achieve international success with its technology. This award evidences the recognition of others and commercial success of the claimed invention.

Applicants also invite the Examiner's attention to a recent, pier-reviewed article validating the Applicants application of the instant technology: Belov et al., "Analysis of Human Leukemias and Lymphomas Using Extensive Immunophenotypes from an Antibody Microarray," 135 British Journal of Haematology, 134-97 (2006) (submitted herewith). In this article, the claimed invention provided for a single assay device in which 82 markers could be studied simultaneously. Over 700 patients were profiled and the levels of consensus for classification using standard criteria were more than 90% accurate. This paper clearly evidences the improvement over any of the techniques addressed in the art cited by the Examiner. In summary, comparing the cited references, in combination, to the claimed invention, it is clear that claimed invention reflects an advancement and "real innovation." *KSR Int'l. Co v. Teleflex Inc.*, No. 04-1350 (April 30, 2007) at 15. Hence, Applicants request that the § 103 rejections be withdrawn.

CONCLUSION

Applicants respectfully request reconsideration of this application and allowance of the pending claims in view of the above remarks.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to char`ge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

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